

EDITORIAL

Clinical significance of post-operative bile reflux gastritis

Bile reflux gastritis is gastritis caused by the enterogastric reflux of bile and other small bowel constituents. It is often defined pathologically as the presence of mononuclear and polymorphonuclear cellular infiltration within the gastric tissues, and graded by the bile reflux index.¹ Endoscopically, bile reflux gastropathy can be seen as the presence of erythema, petechiae, and/or erosions in the gastric mucosa together with the presence of bile. It is well known that gastritis is common after gastrectomy and perhaps after vagotomy and/or pyloroplasty. While some of this gastritis may be due to *Helicobacter pylori* (*H. pylori*) infection, some is likely to be related to bile reflux. In one retrospective study of patients who were followed for one-year post-distal gastrectomy, the prevalence of *H. pylori* infection and bile reflux was both more common in patients with endoscopic gastritis than in those without gastritis. The severity of histologic gastritis was also higher in patients with bile reflux than in those without bile reflux.² Besides gastrectomy, vagotomy, and pyloroplasty, most publications suggested that bile reflux gastritis is also associated with cholecystectomy. In one series, the prevalence of bile reflux gastritis was reported to be as high as 58% among patients who were followed for up to 6 months after cholecystectomy.³ If the association between surgery and bile reflux gastritis is true, one would expect bile reflux gastritis to be increasingly common for the below reasons. Gallstone disease is a highly prevalence disease, with many patients undergoing cholecystectomy for control of their symptoms and complications. Sleeve gastrectomy, and gastric bypass, which are associated with bile reflux gastritis,⁴ are becoming mainstream treatment options for morbid obesity. If post-operative bile reflux gastritis is indeed common or becoming common, the question is what is its clinical implications? In other words, is post-operative bile reflux gastritis a harmless condition or can it be responsible for symptoms, and other long-term upper gastrointestinal mucosal disorders?

Bile reflux non-erosive gastritis is generally considered to be short-lived and not likely to cause dyspepsia. However, a recent retrospective study suggested that bile reflux gastritis could be associated with significant abdominal pain.⁵ The authors found that cholecystectomy was associated with bile reflux gastropathy. Patients with bile reflux gastropathy reported more severe abdominal pain than those with non-bile gastropathy or no gastropathy. In another study among patients who had refractory alkaline reflux gastritis due to a variety of previous gastric surgeries, remedial gastric surgery was found to be effective in relieving symptoms in 87% of these patients,⁶ suggesting that there was a cause-and-effect relationship between bile reflux gastritis, and symptoms. The relationship between bile reflux gastritis and dyspepsia is likely to remain controversial because of several reasons. Firstly, how strictly one defines bile reflux gastritis clinically, endoscopically, histologically, and biochemically is likely to impact on the severity of the reflux, and thus its

resultant injury, and likelihood of causing symptoms. Secondly, some of the dyspeptic symptoms may have nothing to do with the gastritis. Indeed, bile reflux could co-exist with gastro-oesophageal reflux, and some of the upper gastrointestinal symptoms could thus be attributed to gastro-oesophageal reflux disease rather than the gastritis.

Perhaps what is more concerning about bile reflux gastritis is its possible role in causing gastric intestinal metaplasia, in particular intestinal metaplasia at the cardia,^{3,7} which is a precursor of cardia cancer. Indeed, a relationship between cholecystectomy and oesophagogastric junction cancer was shown in a study based on the Finnish Cancer Registry data in 2016.⁸ Some studies also found a significant association between bile reflux and Barrett's oesophagus,⁹ suggesting that bile reflux could aggravate acid reflux in promoting metaplastic changes in the distal oesophagus. If the role of bile in Barrett's oesophagus is real, and since cholecystectomy predisposes to bile reflux, a relationship between cholecystectomy and Barrett's adenocarcinoma should be possible. Indeed, such an association was demonstrated in a population-based cohort study in Sweden crosslinked with the Swedish Cancer Register. Cholecystectomized patients were found to have an increased risk of adenocarcinoma of the oesophagus, and not oesophageal squamous cell carcinoma.¹⁰

The management of bile reflux gastritis depends largely on its aim. If the main issue is dyspepsia, mucoprotective agents such as sucralfate, proton pump inhibitors such as rabeprazole, and prokinetic such as domperidone have all been shown to be effective for symptomatic relief compared with placebos.^{11,12} In treating erosive oesophagitis, or nonerosive nonacidic reflux disease among the post-cholecystectomy patients, it is important to recognise that bile reflux may be the cause, and this condition may not respond as well to the traditional proton pump inhibitor therapy. Mucoprotective agents and prokinetics may be the preferred treatment for this non-acid related condition instead. While the association of bile reflux gastritis with gastric and oesophageal intestinal metaplasia remains to be confirmed, it may be prudent to consider performing opportunistic endoscopic surveillance among the high-risk post-cholecystectomy or post-gastrectomy patients, such as those who are above 50 years of age, or in those who also had past *H. pylori* infection.

With the widespread performance of cholecystectomy, and other surgeries such as obesity surgery, bile reflux gastritis is likely to be an increasingly recognised condition. As it is still a relatively poorly defined condition, this editorial is written with the aim of highlighting the need to conduct further studies; to confirm its predisposing factors, symptomatic role, and its carcinogenic risk. Understanding these issues may have potentially important implications for the prevention of gastric and oesophageal intestinal metaplasia and their associated adenocarcinoma among patients with post-surgical bile reflux gastritis.

Acknowledgments

I would like to thank Professor Ian C Roberts-Thomson for his helpful suggestions for the manuscript.

Khek Yu Ho

Department of Medicine, National University of Singapore

Correspondence

E-mail: khek_yu_ho@nuhs.edu.sg; mdchoky@nus.edu.sg

References

- 1 Sobala GM, O'Connor HJ, Dewar EP, King RF, Axon AT, Dixon MF. Bile reflux and intestinal metaplasia in gastric mucosa. *J. Clin. Pathol.* 1993; **46**: 235–40.
- 2 Li XB, Lu H, Chen HM, Chen XY, Ge ZZ. Role of bile reflux and *Helicobacter pylori* infection on inflammation of gastric remnant after distal gastrectomy. *J. Dig. Dis.* 2008; **9**: 208–12.
- 3 Aprea G, Canfora A, Ferronetti A, Giugliano A, Guida F, Braun A, Battaglini Ciciriello M, Tovecci F, Mastrobuoni G, Cardin F, Amato B. Morpho-functional gastric pre-and post-operative changes in elderly patients undergoing laparoscopic cholecystectomy for gallstone related disease. *BMC Surg.* 2012; **12**: S5.
- 4 Pizza F, D'Antonio D, Lucido FS, Tolone S, Dell'Isola C, Gambardella C. Postoperative Clinical-Endoscopic Follow-up for GERD and Gastritis After One Anastomosis Gastric Bypass for Morbid Obesity: How, When, and Why. *Obes. Surg.* 2020; **30**: 4391–4400.
- 5 Lake A, Rao SSC, Larion S, Spartz H, Kavuri S. Bile reflux gastropathy and functional dyspepsia. *J. Neurogastroenterol Motil.* 2021; **27**: 400–7.
- 6 Zobolas B, Sakorafas GH, Kouroukli I, Glynatsis M, Peros G, Bramis J. Alkaline reflux gastritis: early and late results of surgery. *World J. Surg.* 2006; **30**: 1043–9.
- 7 Dixon MF, Mapstone NP, Neville PM, Moayyedi P, Axon AT. Bile reflux gastritis and intestinal metaplasia at the cardia. *Gut* 2002; **51**: 351–5.
- 8 Rantanen T, Oksala N, Sand J. Adenocarcinoma of the Oesophagus and Oesophagogastric Junction: Analysis of Incidence and Risk Factors. *Anticancer Res* 2016; **36**: 2323–9.
- 9 Dixon MF, Neville PM, Mapstone NP, Moayyedi P, Axon AT. Bile reflux gastritis and Barrett's oesophagus: further evidence of a role for duodenogastro-oesophageal reflux? *Gut.* 2001; **49**: 359–63.
- 10 Freedman J, Ye W, Näslund E, Lagergren J. Gastroenterology. Association between cholecystectomy and adenocarcinoma of the esophagus. *Gastroenterology* 2001; **121**: 548–53.
- 11 Santarelli L, Gabrielli M, Candelli M *et al.* Post-cholecystectomy alkaline reactive gastritis: a randomized trial comparing sucralfate versus rabeprazole or no treatment. *Eur. J. Gastroenterol. Hepatol.* 2003; **15**: 975–9.
- 12 Chen SL, Ji JR, Ping X *et al.* Effect of domperidone therapy on nocturnal dyspeptic symptoms of functional dyspepsia patients. *World J. Gastroenterol.* 2010; **16**: 613–17.